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EDITORIAL

Rethinking energy and protein provision for critically ill patients

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Guidelines informing energy and protein doses for critically ill patients are based largely on low-quality evidence and expert consensus recommendations [1, 2], but more recent randomized controlled trials (RCTs) have provided new data. Thus, we summarize here the current evidence base and provide advice concerning energy and protein provision during critical illness.

Energy dose

To evaluate the best quality evidence regarding energy dose for intensive care unit (ICU) patients, we summarized 'landmark' and/or high-quality RCTs ($n = 9$) investigating energy dose (Supplementary Table 1).

The studies enrolled between 199 and 3036 patients, who were critically ill (range of APACHE II and SOFA scores of 21–23 and 7.1–10.0, respectively). The duration of intervention was approximately 4–28 days in the ICU (median, 7 days). Three studies used indirect calorimetry (IC) to determine the energy requirements [3–5]. The studies achieved target energy delivery on day 1 to 4 after randomization/ICU admission (median, day 2).

Most of the studies found no significant differences in primary outcome between groups, except for two studies [8, 9]. These demonstrated that compared with a lower energy group, the higher energy group had a slower recovery and longer time to readiness for ICU discharge [8, 9]. Higher energy delivery was also found to worsen secondary outcomes including longer duration of organ dysfunction (kidney, liver, lungs) [6, 8, 9], gastrointestinal intolerance (regurgitation, vomiting, constipation, diarrhea) [7, 9, 10], bowel ischemia [9], metabolic intolerance (increased blood glucose level and insulin requirements, lower phosphate level) [5, 7–10], and higher incidence of new infections [8]. One study found a reduction in nosocomial infection between days 9 and 28 in the higher energy group, but this was not significant between days 1 and 28 [4].

Protein dose

A recent systematic review and meta-analysis, including 23 RCTs and 3303 patients, showed that higher vs lower protein doses (average delivered: 1.49 ± 0.48 *vs* 0.92 ± 0.30 g/kg/day) did not significantly improve clinical outcomes [11]. However, higher protein delivery significantly increased mortality rates in a subgroup with acute kidney injury [11]. Although higher protein delivery was associated with attenuation of muscle loss, no clinical or physical-function benefits were found [11]. Recently, the PRECISe trial demonstrated that a high (targeted: 2 g/kg/day; average delivered: 1.48 ± 0.7 g/kg/day) compared with standard (targeted: 1.3 g/kg/day; average delivered: 0.95 ± 0.44 g/kg/day) protein delivery significantly decreased EuroQol-5 Dimensions-5 Levels [EQ-5D-5L] up to day 180 [12]. The level of evidence supporting a protein dose of 1.3 g/kg is currently limited.

Learning points and proposed energy/protein provision

Based on current evidence, achieving higher energy and/or protein delivery early (days 1–7) during critical illness does not generally improve clinical outcomes. The signal of worse clinical/gastrointestinal/metabolic outcomes with higher energy and/or protein delivery during this early period, may be a physiological indication that excessive macronutrients cannot be used effectively and may instead increase the load on failing organs. Thus, early high-dose nutrition should be avoided in patients with severe illness/multi-organ failure [9, 13]. However,

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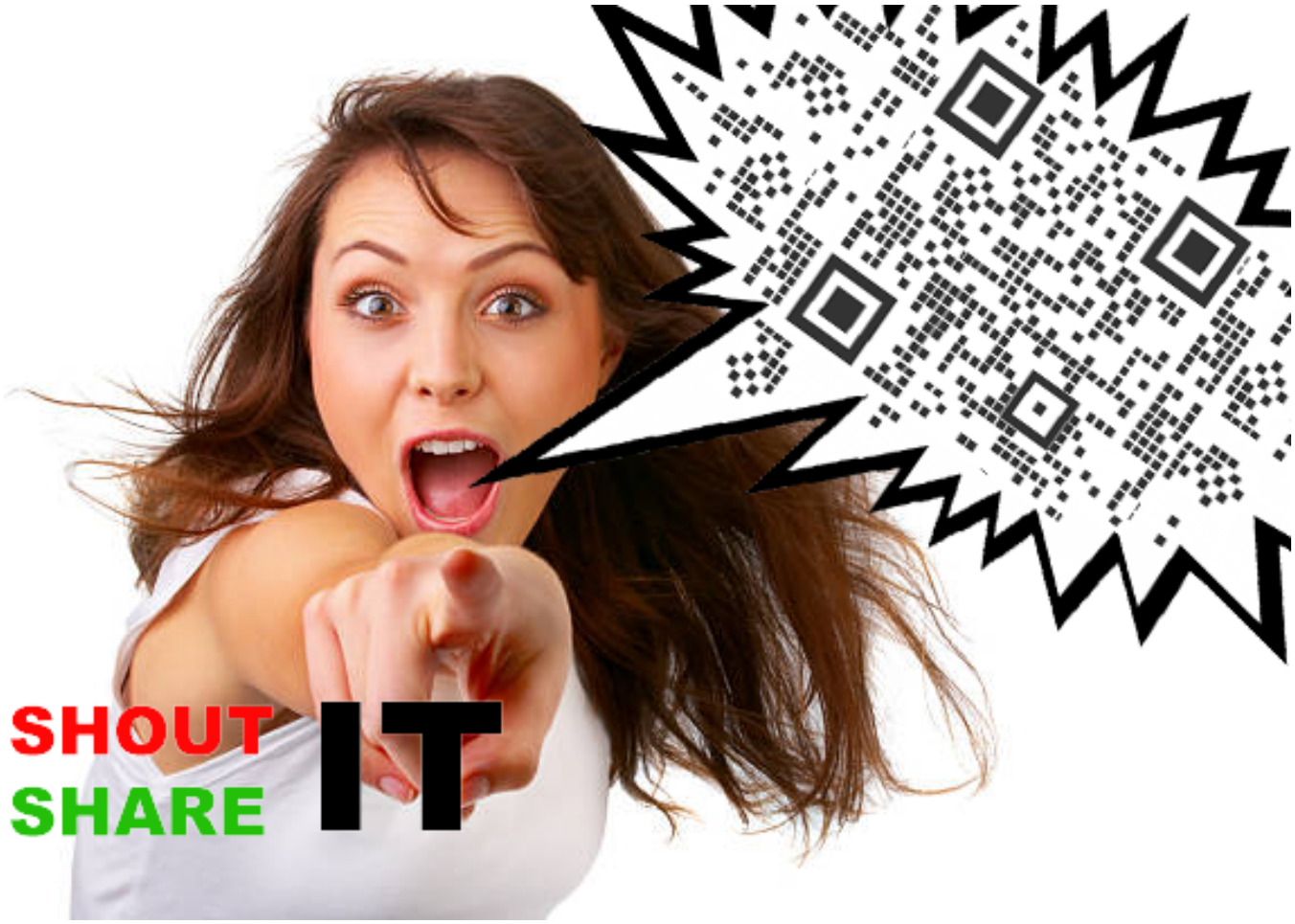
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prolonged underfeeding (e.g. > 1–2 weeks with very low energy/protein doses in stabilized patients) may also be harmful, aggravating muscle wasting and limiting patients' functional recovery.

Based on our interpretation of current high-quality RCTs, we suggest progressive feeding be given based on both days spent in the ICU and considering the patients' clinical severity status (e.g. vasopressor requirements and level of organ support) (Fig. 1). We suggest feeding up to 5–10 kcal/kg and 0.2–0.6 g/kg protein during the first 4 days of critical illness as (i) the lowest tolerated energy and protein doses investigated were 5 kcal/kg and 0.2 g/kg, respectively [8–10]; (ii) energy and protein targets were achieved on days 1 to 4 in the studies included; and (iii) a minimum difference of 5 kcal/kg and 0.4 g/kg protein between groups seems to have an effect on patients' outcomes. From days 5–7, we suggest progressive incremental feeding of up to 15–20 kcal/kg and 0.8–1.0 g/kg protein, to avoid prolonged underfeeding in patients who are stable/not deteriorating (on low-dose/maintenance level of organ support) or who are recovering (reducing levels of organ support), pending stronger evidence. After day 7, we suggest a careful dose of 20–25 kcal/kg and 1.0–1.2 g/kg protein; however, data are lacking on doses beyond day 7. We suggest careful monitoring of metabolic status and readiness as follows: reduce energy doses if either phosphate levels decrease by at least 0.16 mmol/L (to < 0.65 mmol/L|) within 72 h of feeding [14], if blood glucose level rises (to > 10 mmol/L) despite adequate insulin treatment, or in cases of acute severe hypertriglyceridemia (> 4.5 mmol/L) (Supplementary references 14 and 15). We suggest reducing protein doses if urea levels increase two-fold from baseline levels [15] whilst creatinine levels remain stable. In addition, adjusting protein dose to not more than 0.8 g/kg/day if renal replacement therapy is not planned following a diagnosis of acute kidney injury [11].

Regardless of days spent in the ICU, we suggest reducing energy and protein dose (to a maximum of 5–10 kcal/kg/day or 0.2–0.6 g/kg protein/day) if a new acute deterioration occurs (i.e. increasing number or dosage of vasopressors, or worsening organ failure status). Moreover, when monitoring total energy dose, it is important to account for non-nutritional energy sources (e.g. propofol,

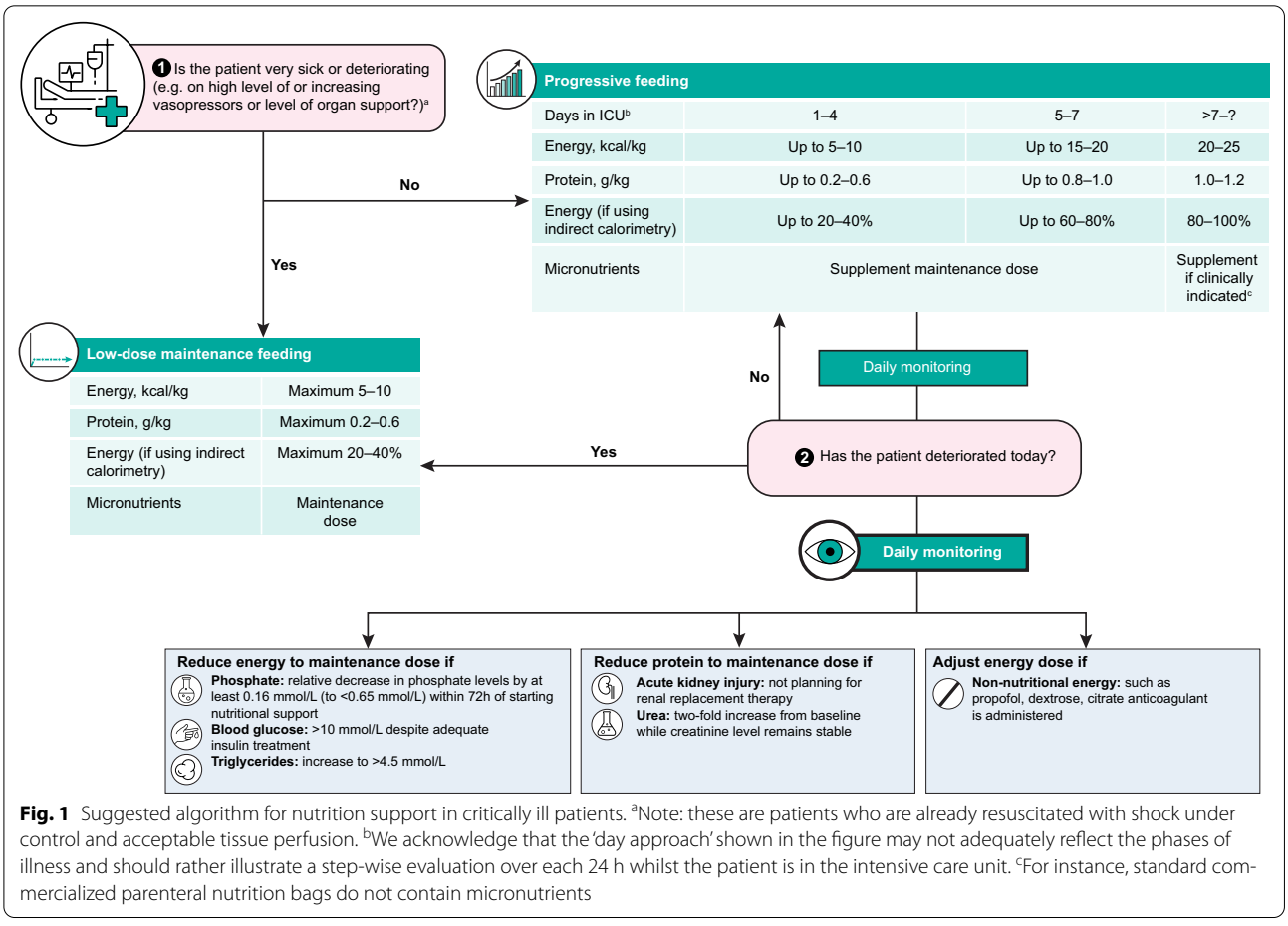
1 Is the patient very sick or deteriorating (e.g. on high level of or increasing vasopressors or level of organ support?)[a]
No
Yes
Progressive feeding
Days in ICU[b] | 1–4 | 5–7 | >7–?
Energy, kcal/kg | Up to 5–10 | Up to 15–20 | 20–25
Protein, g/kg | Up to 0.2–0.6 | Up to 0.8–1.0 | 1.0–1.2
Energy (if using indirect calorimetry) | Up to 20–40% | Up to 60–80% | 80–100%
Micronutrients | Supplement maintenance dose | | Supplement if clinically indicated[c]
Low-dose maintenance feeding
Energy, kcal/kg | Maximum 5–10
Protein, g/kg | Maximum 0.2–0.6
Energy (if using indirect calorimetry) | Maximum 20–40%
Micronutrients | Maintenance dose
No
Yes
Daily monitoring
2 Has the patient deteriorated today?
Daily monitoring
Reduce energy to maintenance dose if
Phosphate: relative decrease in phosphate levels by at least 0.16 mmol/L (to <0.65 mmol/L) within 72h of starting nutritional support
Blood glucose: >10 mmol/L despite adequate insulin treatment
Triglycerides: increase to >4.5 mmol/L
Reduce protein to maintenance dose if
Acute kidney injury: not planning for renal replacement therapy
Urea: two-fold increase from baseline while creatinine level remains stable
Adjust energy dose if
Non-nutritional energy: such as propofol, dextrose, citrate anticoagulant is administered

Fig. 1 Suggested algorithm for nutrition support in critically ill patients. [a]Note: these are patients who are already resuscitated with shock under control and acceptable tissue perfusion. [b]We acknowledge that the 'day approach' shown in the figure may not adequately reflect the phases of illness and should rather illustrate a step-wise evaluation over each 24 h whilst the patient is in the intensive care unit. [c]For instance, standard commercialized parenteral nutrition bags do not contain micronutrients

dextrose or citrate anticoagulants). Notably, our proposal is consistent and further adds to the viewpoints and interpretations expressed in recent expert papers (Supplementary references 16 and 17).

Limitations and future directions

The optimal energy and protein dose for critically ill patients during the course of critical illness remains unknown. Areas of uncertainty include the use of IC, clinical cut-offs to describe clinical conditions and/or biomarkers to define critical illness phases, and metabolic tolerance and readiness for nutrition. Therefore, the best time to switch to full feeding for optimizing patients' nutritional status cannot be determined precisely yet. Further study is needed to determine whether complete fasting *vs* low-dose nutrition helps recovery in the first few days of critical illness or when high/increasing levels of organ support are indicated. Advances in precision or personalized medicine (using, for example, latent class analysis or machine-learning models) are ongoing in critical care (Supplementary references 18 and 19), and these should include nutritional aspects. These methods may help identify those patients most likely to benefit and others who might potentially be harmed from particular nutritional interventions.

Conclusions

In critically ill patients, we suggest that energy and protein be delivered progressively in stable or recovering patients. If a patient deteriorates, regardless of days spent in the ICU, low-dose energy and protein should be delivered to maintain basic body functions until stabilized. More research is underway to advance precision nutrition within critical care, adapting to individual needs by assessing each patient's metabolic state, inflammatory status, and degree of organ dysfunction.

Supplementary Information
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